Quest for the best : quality of colonoscopy and colorectal cancer diagnosis in clinical practice

&

Valorisation

Dutch universities have three main tasks: to educate at an academic level, to conduct scholarly research and to ensure that research findings impact society.[1] Valorisation is the term that governmental and university policymakers use to denote the process of "translating academic wisdom to societal benefit." This chapter is intended to translate the scientific findings of this thesis into applicable prospects for society. This thesis provides relevant new aspects and views on quality of colonoscopy and on colorectal carcinogenesis relevant for several stakeholders: first to patients, but also to health care providers and organizations involved in developing guidelines.

As described in **Chapter 1**, colorectal cancer (CRC) had a major impact worldwide also in The Netherlands, where annually 15,000 patients are diagnosed with the disease.[2] This number will even increase with the start of the fecal test based population based nationwide CRC screening program.[3] In view of this screening program, the quality of colonoscopy is key since all patients with an unfavourable fecal test result will undergo colonoscopy. Herein colonoscopy is our best available modality to detect CRC. Although generally considered as the golden standard, colonoscopy is not and cancers are being missed at colonoscopy. Suboptimal colonoscopy quality will decrease the benefit of screening programs both from a clinical and financial perspective. It is important to inform patients also about the limitations of colonoscopy. Even in experienced hands, it is not a 100% perfect diagnostic and therapeutic method. Thus, apart from being informed about the risk of perforation and bleeding during colonoscopy, a patient should also be informed about the value of the technique and the potential risk of postcolonoscopy (interval) CRCs.

In order to evaluate the current colonoscopic quality in South-Limburg, the Netherlands prior to commencing CRC screening, we conducted several studies in regional collaboration that have described in **Chapters 3, 4, 6** and **7**. The findings of these studies, first of all, show the quality at baseline is already of adequate standard, with low incidence rates of postcolonoscopy CRC (i.e. 2/1,000 colonoscopies or 2.9% of all CRC patients) and metachronous CRC compared to other studies[4,5] and with colonoscopic quality indicators who meet international standards.[6] These data are reassuring and in general should be available for patients, community and the various stakeholders. Second, the cases in which CRC was missed (i.e. postcolonoscopy CRC cases) were most likely related to procedural factors. These procedural factors are amendable for improvement by training of the endoscopist, by adhering to surveillance guidelines and by strengthening the importance of adequate bowel preparation to patients. The results on the origin of postcolonoscopy CRC and recommendations described in **Chapter 3**, are cited and distributed among patients,[7] health care providers,[3] organizations involved in developing guidelines,[8] and among scientist.[9-11] More importantly, the results are incorporated into new Dutch guidelines on colonoscopy surveillance[8] and national training modules such as the e-learning module for certification of endoscopists in the bowel cancer screening program.[3]

The results on colonoscopic quality described in this thesis form the basis for CRC screening in South-Limburg. With the implementation of e-learning module with specific attention for the detection of nonpolypoid lesions, the colonoscopic quality will further improve within the screening program, in our region but also nationwide in the Netherlands. Monitoring of each 'failure', with use of uniform nomenclature (**Chapter 5**) and evaluation of the potential origin of these missed CRCs, will further improve overall quality.

In addition this thesis presents more detailed insight on the colonoscopic quality of patients with a history of CRC. These patient will undergo lifelong colonoscopic surveillance in order to detect recurrences or metachronous CRCs. The results described in **Chapter 4** show the quality of colonoscopic surveillance in this group of patients is open for improvement. The incidence of metachronous CRC was relatively low compared to other studies,[5] but it was not zero. The majority of these metachronous CRCs are related to missed lesions and to non-adherence to surveillance guidelines. Therefore, in 2013, in the Netherlands a new guideline has been published for the surveillance of CRC survivors, underscoring the importance of quality colonoscopy in this group of patients.[8]

Prior the start of the studies described in this thesis, the main research question was whether postcolonoscopy CRCs were related to technology (procedural factors) or merely biology (new cancers). Over time, exploring the data in more detail, it became evident to us and others,[12,13] that the main explanation of postcolonoscopy CRCs is technology (in fact: missed lesions) . In contrast, some studies showed a difference in molecular make-up of postcolonoscopy CRCs compared to prevalent CRCs,[14,15] leaving room for debate. The data described in this thesis point towards a combination of factors: both technology and biology related. We have shown postcolonoscopy CRCs are missed lesions in 58% of cases. These cancers show subtle (flat and small) morphology and are located primarily in the proximal colon, factors by which they are easily missed, but also factors related to different carcinogenesis such as the involvement of the serrated pathway. By analysing each postcolonoscopy cancer case thoroughly, including DNA mutation analyses, we will further unravel the roles of technology, biology and its combination.

In short, the data presented in this thesis emphasize the high quality of the Dutch colonoscopy practice. We have pointed to potential causes for the occurrence of postcolonoscopy cancers as the majority were related to avoidable causes that provide room for improvement. These improvements (with specialo attention to the detection and removal of right sided located flat polyps, quality of bowel preparation, compliance with the surveillance guidelines) have already been incorporated into local, national and international guidelines and e-learning modules. In the future, the results on incidence, etiology of postcolonoscopy, interval, and metachronous CRCs occurring within the

screening program, will further increase our knowledge and understanding of the disease. Especially the knowledge on the role of its biology will shed light on colorectal carcinogenesis in the near future.

References

1. Drooge vL, Meulen vdB. Valorisatie als feitelijke kerntaak van de universiteiten. 2012:
2. IKNL. Integraal Kankercentrum Nederland. Cijfers over kanker In: http://www.cijfersover-kanker.nl/selecties/Dataset_1/img5618e12066148; 2015
3 National Institute for Public Health and the Environment, Bowel cancer screening programme, 2014, http://www.rivm.nl/en/Topics/B/Bowel_cancer_screening_programme
4. Singh S, Singh PP, Murad MH, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol 2014; 109: 1375-1389
5. Mulder SA, Kranse R, Damhuis RA, Ouwendijk RJ, Kuipers EJ, van Leerdam ME. The incidence and risk factors of metachronous colorectal cancer: an indication for follow-up. Dis Colon Rectum 2012; 55: 522-531
6. Gavin DR, Valori RM, Anderson JT, Donnelly MT, Williams JG, Swarbrick ET. The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK. Gut 2013; 62: 242-249
7. Maag Darm Lever Stichting. Nederlandse studie naar kijkonderzoek bij darmkanker wint internationaal hoog aanzien. www.mlds.nl; 2015
8. Nederlandse Vereniging van Maag-, Darm- en Leverartsen. Nederlandse Richtlijn Coloscopie Surveillance. 2013
9. Haug U, Regula J. Interval cancer: nightmare of colonoscopists. Gut 2014; 63: 865-866
10. McGill SK, Kaltenbach T, Friedland S, Soetikno R. The learning curve for detection of non-polypoid (flat and depressed) colorectal neoplasms. Gut 2015; 64: 184-185
11. Dominitz JA, Robertson DJ. Interval cancers: learning from the past as we build for the future. Am J Gastroenterol 2013; 108: 1341-1343
12. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative colonoscopy: population-based case-control study. Gut 2012; 61: 1576-1582
13. Robertson DJ, Lieberman DA, Winawer SJ, Ahnen DJ, Baron JA, Schatzkin A, Cross AJ, Zauber AG, Church TR, Lance P, Greenberg ER, Martinez ME. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut 2014; 63: 949-956
14. Cisyk AL, Singh H, McManus KJ. Establishing a biological profile for interval colorectal cancers. Dig Dis Sci 2014; 59: 2390-2402
15. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013; 369: 1095-1105